L Number	Hits	Search Text	DB	Time stamp
4	12	Ruvkun NEAR Gary	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/01/21 11:45
5	174	DAF-$5	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/01/21 11:51
6	9	DAF-$5 and DAF-18	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/01/21 11:51
8	617	glucose AND diabet$5 AND obes$10 AND elegans	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/01/21 11:52
9	20	DAF-$5 and (glucose AND diabet$5 AND obes$10 AND elegans)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/01/21 11:57
11	490	PTEN	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/01/21 11:59
12	12	DAF-$5 and PTEN	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/01/21 11:59
13	9	daf-18	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/01/21 12:00
14	131	PTEN and transgenic	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/01/21 12:12
15	40	(PTEN and transgenic) and elegans	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/01/21 12:07
17	48	PTEN and elegans	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/01/21 12:07
18	21	PTEN and transgenic.clm.	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/01/21 12:12

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     (FILE 'HOME' ENTERED AT 13:22:25 ON 21 JAN 2004)

     FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED
     AT 13:22:44 ON 21 JAN 2004
L1          7816 S DAF? OR DAF-18 OR DAF18
L2          4962 S PTEN OR MMAC1 OR TEP1
L3            29 S L1 AND L2
L4            13 DUP REM L3 (16 DUPLICATES REMOVED)
L5            13 SORT L4 PY
L6           127 S L2 AND TRANSGENIC
L7            59 DUP REM L6 (68 DUPLICATES REMOVED)
L8             2 S L7 AND (NEMATODE? OR ELEGANS)
L9            62 S L2 AND (NEMATODE? OR ELEGANS)
L10           41 DUP REM L9 (21 DUPLICATES REMOVED)
L11            3 S L10 AND TRANSGEN?
                 E RUVKUN G?/AU
L12           95 S E4
L13            2 S L12 AND L3
L14            2 DUP REM L13 (0 DUPLICATES REMOVED)

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L14  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2000:384548  CAPLUS
DN   133:39116
TI   Genes and polypeptides involved in insulin signaling pathways for glucose
     tolerance, obesity, and longevity and their uses as therapeutic and
     diagnostic tools
SO   PCT Int. Appl., 402 pp.
     CODEN: PIXXD2
IN   Ruvkun, Gary; Ogg, Scott
AB   Disclosed herein are novel genes and methods for the screening of
     therapeutics useful for treating impaired glucose tolerance conditions, as
     well as diagnostics and therapeutic compns. for identifying or treating
     such conditions.  The Caenorhabditis elegans metabolic regulatory genes
     daf-2 and age-1 encode homologs of the mammalian insulin
     receptor/phosphoinositol 3-kinase signaling pathway proteins, resp.  Also,
     the C. elegans PKB kinase and AKT kinase act downstream of these genes, as
     their mammalian homologs act downstream of insulin signaling.  The C.
     elegans PTEN lipid phosphatase homolog, DAF-18
     , acts upstream of AKT in this signaling pathway.  Further, the
     DAF-16 forkhead protein represents the major transcriptional
     output of this insulin signaling pathway.  Addnl. evidence indicates that
     the DAF-16, DAF-3, DAF-8, and DAF
     -14 transcriptional outputs of converging signaling pathways regulate
     metab.  The congruence between the C. elegans and mammalian insulin
     signaling pathways strongly supports the contention that new genes
     identified in the C. elegans pathway also act in mammalian insulin
     signaling.  Exemplary sequences and functional characteristics of the C.
     elegans daf genes and their human homologs are provided.
     PATENT NO.         KIND  DATE           APPLICATION NO.  DATE
     ---------------    ----  --------       ---------------  --------
PI   WO 2000033068      A1    20000608       WO 1999-US28529  19991202
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
             CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
             IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
             MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
             SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ,
             BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
             DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
             CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     US 2001029617      A1    20011011       US 1998-205658   19981203
     EP 1163515         A1    20011219       EP 1999-960641   19991202
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
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L14 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:37224 CAPLUS
DN 130:220650
TI The C. elegans **PTEN** homolog, **DAF-18**, acts in the insulin receptor-like metabolic signaling pathway
SO Molecular Cell (1998), 2(6), 887-893
CODEN: MOCEFL; ISSN: 1097-2765
AU Ogg, Scott; **Ruvkun, Gary**
AB An insulin-like signaling pathway, from the **DAF**-2 receptor, the AGE-1 phosphoinositide 3-kinase, and the AKT-1/AKT-2 serine/threonine kinases to the **DAF**-16 Fork head transcription factor, regulates the metab., development, and life span of Caenorhabditis elegans. Inhibition of **daf-18** gene activity bypasses the normal requirement for AGE-1 and partially bypasses the need for **DAF**-2 signaling. The suppression of age-1 mutations by a **daf-18** mutation depends on AKT-1/AKT-2 signaling, showing that **DAF-18** acts between AGE-1 and the AKT input to **DAF**-16 transcriptional regulation. **Daf-18** encodes a homolog of the human tumor suppressor **PTEN** (**MMAC1/TEP1**), which has 3-phosphatase activity toward phosphatidylinositol 3,4,5-trisphosphate (PIP3). **DAF-18** **PTEN** may normally limit AKT-1 and AKT-2 activation by decreasing PIP3 levels. The action of **daf-18** in this metabolic control pathway suggests that mammalian **PTEN** may modulate insulin signaling and may be variant in diabetic pedigrees.

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(FILE 'HOME' ENTERED AT 13:22:25 ON 21 JAN 2004)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 13:22:44 ON 21 JAN 2004

L1 7816 S DAF? OR DAF-18 OR DAF18
L2 4962 S PTEN OR MMAC1 OR TEP1
L3 29 S L1 AND L2
L4 13 DUP REM L3 (16 DUPLICATES REMOVED)
L5 13 SORT L4 PY

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=> d an ti so au ab pi l5 7 1-4 12

L5 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:384548 CAPLUS
DN 133:39116
TI Genes and polypeptides involved in insulin signaling pathways for glucose tolerance, obesity, and longevity and their uses as therapeutic and diagnostic tools
SO PCT Int. Appl., 402 pp.
CODEN: PIXXD2
IN Ruvkun, Gary; Ogg, Scott
AB Disclosed herein are novel genes and methods for the screening of therapeutics useful for treating impaired glucose tolerance conditions, as well as diagnostics and therapeutic compns. for identifying or treating such conditions. The Caenorhabditis elegans metabolic regulatory genes **daf**-2 and age-1 encode homologs of the mammalian insulin receptor/phosphoinositol 3-kinase signaling pathway proteins, resp. Also, the C. elegans PKB kinase and AKT kinase act downstream of these genes, as their mammalian homologs act downstream of insulin signaling. The C. elegans **PTEN** lipid phosphatase homolog, **DAF-18** , acts upstream of AKT in this signaling pathway. Further, the **DAF**-16 forkhead protein represents the major transcriptional output of this insulin signaling pathway. Addnl. evidence indicates that the **DAF**-16, **DAF**-3, **DAF**-8, and **DAF** -14 transcriptional outputs of converging signaling pathways regulate metab. The congruence between the C. elegans and mammalian insulin signaling pathways strongly supports the contention that new genes identified in the C. elegans pathway also act in mammalian insulin signaling. Exemplary sequences and functional characteristics of the C. elegans **daf** genes and their human homologs are provided.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000033068	A1	20000608	WO 1999-US28529	19991202
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2001029617	A1	20011011	US 1998-205658	19981203
EP 1163515	A1	20011219	EP 1999-960641	19991202
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

L5 ANSWER 1 OF 13 MEDLINE on STN
AN 1999102962 MEDLINE
TI The C. elegans **PTEN** homolog, **DAF-18**, acts in the insulin receptor-like metabolic signaling pathway.
SO MOLECULAR CELL, (1998 Dec) 2 (6) 887-93.
Journal code: 9802571. ISSN: 1097-2765.
AU Ogg S; Ruvkun G
AB An insulin-like signaling pathway, from the **DAF**-2 receptor, the

AGE-1 phosphoinositide 3-kinase, and the AKT-1/AKT-2 serine/threonine kinases to the **DAF**-16 Fork head transcription factor, regulates the metabolism, development, and life span of Caenorhabditis elegans. Inhibition of **daf-18** gene activity bypasses the normal requirement for AGE-1 and partially bypasses the need for **DAF**-2 signaling. The suppression of age-1 mutations by a **daf-18** mutation depends on AKT-1/AKT-2 signaling, showing that **DAF-18** acts between AGE-1 and the AKT input to **DAF**-16 transcriptional regulation. **daf-18** encodes a homolog of the human tumor suppressor **PTEN** (**MMAC1/TEP1**), which has 3-phosphatase activity toward phosphatidylinositol 3,4,5-trisphosphate (PIP3). **DAF-18** **PTEN** may normally limit AKT-1 and AKT-2 activation by decreasing PIP3 levels. The action of **daf-18** in this metabolic control pathway suggests that mammalian **PTEN** may modulate insulin signaling and may be variant in diabetic pedigrees.

L5 ANSWER 2 OF 13 MEDLINE on STN
AN 1999307426 MEDLINE
TI The **PTEN** tumor suppressor homolog in Caenorhabditis elegans regulates longevity and dauer formation in an insulin receptor-like signaling pathway.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Jun 22) 96 (13) 7427-32.
Journal code: 7505876. ISSN: 0027-8424.
AU Mihaylova V T; Borland C Z; Manjarrez L; Stern M J; Sun H
AB Inactivation of the tumor suppressor **PTEN** gene is found in a variety of human cancers and in cancer predisposition syndromes. Recently, **PTEN** protein has been shown to possess phosphatase activity on phosphatidylinositol 3,4,5-trisphosphate, a product of phosphatidylinositol 3-kinase. We have identified a homolog of **PTEN** in Caenorhabditis elegans and have found that it corresponds to the **daf-18** gene, which had been defined by a single, phenotypically weak allele, **daf-18**(e1375). By analyzing an allele, **daf-18**(nr2037), which bears a deletion of the catalytic portion of CePTEN/**DAF-18**, we have shown that mutation in **daf-18** can completely suppress the dauer-constitutive phenotype caused by inactivation of **daf**-2 or age-1, which encode an insulin receptor-like molecule and the catalytic subunit of phosphatidylinositol 3-kinase, respectively. In addition, **daf-18**(nr2037) dramatically shortens lifespan, both in a wild-type background and in a **daf**-2 mutant background that normally prolongs lifespan. The lifespan in a **daf -18**(nr2037) mutant can be restored to essentially that of wild type when combined with a **daf**-2 mutation. Our studies provide genetic evidence that, in C. elegans, the **PTEN** homolog **DAF-18** functions as a negative regulator of the **DAF**-2 and AGE-1 signaling pathway, consistent with the notion that **DAF-18** acts a phosphatidylinositol 3,4,5-trisphosphate phosphatase in vivo. Furthermore, our studies have uncovered a longevity-promoting activity of the **PTEN** homolog in C. elegans.

L5 ANSWER 3 OF 13 MEDLINE on STN
AN 1999227332 MEDLINE
TI Regulation of dauer larva development in Caenorhabditis elegans by **daf-18**, a homologue of the tumour suppressor **PTEN**.
SO CURRENT BIOLOGY, (1999 Mar 25) 9 (6) 329-32.
Journal code: 9107782. ISSN: 0960-9822.
AU Rouault J P; Kuwabara P E; Sinilnikova O M; Duret L; Thierry-Mieg D; Billaud M
AB The tumour suppressor gene **PTEN** (also called **MMAC1** or **TEP1**) is somatically mutated in a variety of cancer types [1] [2] [3] [4]. In addition, germline mutation of **PTEN** is responsible for two dominantly inherited, related cancer syndromes called Cowden disease and Bannayan-Ruvalcaba-Riley syndrome [4]. **PTEN** encodes a dual-specificity phosphatase that inhibits cell spreading and migration partly by inhibiting integrin-mediated signalling [5] [6] [7]. Furthermore, **PTEN** regulates the levels of phosphatidylinositol

3,4,5-trisphosphate (PIP3) by specifically dephosphorylating position 3 on the inositol ring [8]. We report here that the dauer formation gene **daf-18** is the Caenorhabditis elegans homologue of **PTEN**. **DAF-18** is a component of the insulin-like signalling pathway controlling entry into diapause and adult longevity that is regulated by the **DAF**-2 receptor tyrosine kinase and the AGE-1 PI 3-kinase [9]. Others have shown that mutation of **daf-18** suppresses the life extension and constitutive dauer formation associated with **daf**-2 or age-1 mutants. Similarly, we show that inactivation of **daf-18** by RNA-mediated interference mimics this suppression, and that a wild-type **daf-18** transgene rescues the dauer defect. These results indicate that **PTEN/daf-18** antagonizes the **DAF**-2-AGE-1 pathway, perhaps by catalyzing dephosphorylation of the PIP3 generated by AGE-1. These data further support the notion that mutations of **PTEN** contribute to the development of human neoplasia through an aberrant activation of the PI 3-kinase signalling cascade.

L5 ANSWER 4 OF 13 MEDLINE on STN
AN 1999178991 MEDLINE
TI Regulation of the insulin-like developmental pathway of Caenorhabditis elegans by a homolog of the **PTEN** tumor suppressor gene.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Mar 16) 96 (6) 2925-30.
Journal code: 7505876. ISSN: 0027-8424.
AU Gil E B; Malone Link E; Liu L X; Johnson C D; Lees J A
AB The human **PTEN** tumor suppressor gene is mutated in a wide variety of sporadic tumors. To determine the function of **PTEN** in vivo we have studied a **PTEN** homolog in Caenorhabditis elegans. We have generated a strong loss-of-function allele of the **PTEN** homolog and shown that the deficient strain is unable to enter dauer diapause. An insulin-like phosphatidylinositol 3-OH kinase (PI3'K) signaling pathway regulates dauer-stage entry. Mutations in either the **daf**-2 insulin receptor-like (IRL) gene or the age-1 encoded PI3'K catalytic subunit homolog cause constitutive dauer formation and also affect the life span, brood size, and metabolism of nondauer animals. Strikingly, loss-of-function mutations in the age-1 PI3'K and **daf**-2 IRL genes are suppressed by loss-of-function mutations in the **PTEN** homolog. We establish that the **PTEN** homolog is encoded by **daf-18**, a previously uncloned gene that has been shown to interact genetically with the **DAF**-2 IRL AGE-1 PI3'K signaling pathway. This interaction provides clear genetic evidence that **PTEN** acts to antagonize PI3'K function in vivo. Given the conservation of the PI3'K signaling pathway between C. elegans and mammals, the analysis of **daf-18 PTEN** mutant nematodes should shed light on the role of human **PTEN** in the etiology of metabolic disease, aging, and cancer.

L5 ANSWER 12 OF 13 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
AN 2003:79971 SCISEARCH
TI Life span extensions associated with upregulation of gene expression of antioxidant enzymes in Caenorhabditis elegans, studies of mutation in the age-1, PI3 kinase homologue and short-term exposure to hyperoxia.
SO JOURNAL OF THE AMERICAN AGING ASSOCIATION, (JAN 2002) Vol. 25, No. 1, pp. 21-28.
Publisher: AMER AGING ASSOC, SALLY BALIN MEDICAL CENTER, 110 CHESLEY DR, MEDIA, PA 19063 USA.
ISSN: 0161-9152.
AU Honda Y; Honda S (Reprint)
AB Life span could be modified by genetic or environmental perturbations in Caenorhabditis elegans. Here we show that two extensions of life span are associated with oxidative stress resistance and upregulation of the gene expression of antioxidant enzymes. First, mutations in age-1 gene (PI3 kinase homologue) that confer life span extension, display oxidative stress resistance and increase in the gene expression of sod-3, one of two Mn-superoxide dismutases (SOD) and ctl-1, cytosolic catalase. In this study, these traits appear to be regulated by the following genetic pathway: **daf**-2 (insulin receptor family) -> **daf**-

18 (**PTEN** homologue) -> age-1 -> **daf**-16 (Fork head transcription factor family), similar to the genetic pathway for the life span extension. Second, we show that short-term exposure to hyperoxia extends life span slightly but significantly. This treatment increases oxidative stress resistance and the gene expression of three types of SOD isoforms. These results suggest that both of these two life span extensions are closely related with increase in the antioxidant defense function.

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09205658: Interference and Seq search

Title: THERAPEUTIC AND DIAGNOSTIC TOOLS FOR IMPAIRED GLUCOSE TOLERANCE CONDITIONS

Inventor: RUVKUN, GARY

Please search

SEQ ID NO: 309
SEQ ID NO: 310

S. Kaushal
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